REMARKS

The foregoing amendments and the following remarks are submitted for entry and consideration in response to the communication dated January 12, 2006.

Status of the Claims

Claims 14-17 are pending in the application. Claims 14, 15, 16 and 17 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amended claims can be found generally through Applicants' Specification.

The Double Patenting Rejections

The Examiner has provisionally rejected claims 14-17 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-17 of copending Application Serial No. 10/443,663 ("the '663 Application"). Applicants point out that the '663 Application is a copending application of Applicants and has recently initiated formal prosecution. In as much as this rejection is provisional, Applicants acknowledge this rejection and recognize it as provisional at present. The issue will readdressed by Applicants at such time as other patentability issues are settled.

The Examiner has further provisionally rejected claims 14-17 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-17 of copending Application Serial No. 11/029,763 ("the '763 Application"). Applicants point out that the '763 Application is a copending application of Applicants and has begun formal prosecution. Applicants further underscore that, in a Response mailed May 25, 2006 to an outstanding restriction requirement in the '763 Application, claims in a different group, patentably distinct from claims 14-17 were elected and claims 14-17 are effectively withdrawn. In as much as claims 14-17 are effectively withdrawn in the '763 Application, being directed to a non-elected invention, Applicants request that this provisional double patenting rejection be withdrawn.

The 35 U.S.C. 112, First Paragraph, Rejection

Claims 14-17 are again rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is set out as a new matter rejection, the Examiner asserting that the recitation "and do not give rise to functional gametes" is considered new matter because there is no description in the Specification for a pluripotent embryonic-like stem cell that does not give rise to functional gametes. In conjunction with this rejection, again to the extent that the Examiner asserts that claimed compositions and/or methods are not described in the instant disclosure, the Examiner rejects claims 14-17 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the Specification as to enable the skilled artisan to make and/or use the invention. Applicants respectfully disagree and submit that the Specification provides support for and describes pluripotent embryonic-like stem cells, which by definition and in character are not totipotent cells and thereby do not give rise to functional gametes. In addition, the Specfication, particularly when combined with the significant skill and knowledge of the skilled artisan, enables the skilled artisan to make and/or use the invention and the claimed genetically engineered stem cells.

The pluripotent embryonic-like stem cells of the invention are pluripotent and NOT totipotent. A pluripotent cell, by nature and recognized definition, is <u>not</u> totipotent. A totipotent cell, by nature and recognized definition, is a stem cell capable of forming every type of body cell, including both somatic cells and gametes. While a totipotent cell has all the differentiative capabilities of a pluripotent cell and more (being also able to form gametes, etc.), a pluripotent cell has only a subset of or certain of the differentiative capacities of a totipotent cell. A pluripotent cell is more limited in capacity than a totipotent cell. The Specification teaches, including at page 3, lines 29-31, that embryonic stem cells are "totipotent", giving rise to all somatic lineages as well as functional gametes. This text does not refer to a totipotent zygote, as suggested by the Examiner, it refers to totipotent cells, as exemplified particularly by embryonic stem (ES) cells, which "can give rise to all somatic lineages as well as functional gametes". In contrast, the claimed "pluripotent" embryonic-like stem cells are <u>pluripotent</u>. The Examiner, in his remarks on page 5 of the Office Action, quotes from a definition of totipotent from the NIH website. Applicants point out that this definition states the following:

> Totipotent—Having unlimited capability. The totipotent cells of the very early embryo have the capacity to differentiate into extra embryonic membranes and tissues, the embryo, and all postembryonic tissues and organs.

This definition has reference to totipotent cells of the "very early embryo". Applicants also reference a web site definition (www.meta-library.net/biogloss/totistem-body.html) which states particularly:

> All cells within the early embryo are totipotent up until the 16 cell stage or so.

ES cells are cells of the embryo, isolated from the blastocyst, inner cell mass or gonadal ridges (see for instance the Specification at page 4, lines 4-8). Importantly and in contrast, Applicants' PPELSCs are pluripotent cells derived from non-embryonic or postnatal animal cells or tissues. It would, certainly, be surprising and notable for a cell or cells derived from non-embryonic or postnatal cells or tissues to have totipotent capabilities. A pluripotent cell is not presumed to have totipotent capacity. The skilled artisan or other knowledged individual would expect, including from a reading of the Specification, a pluripotent cell to lack the ability to form gametes. In fact, a pluripotent cell is recognized as being derived from or differentiated from a totipotent cell as noted in the public domain at www.medterms.com/script/main/art.asp?articlekey=18261 where it is stated:

> Totipotent is as opposed to pluripotent and multipotent. Totipotent cells have total potential. They specialize into pluripotent cells that can give rise to most, but not all, of the tissues necessary for fetal development. Pluripotent cells undergo further specialization into multipotent cells that are committed to give rise to cells that have a particular function. For example, multipotent blood stem cells give rise to the red cells, white cells and platelets in the blood.

The Examiner further remarks that Applicants' arguments are not persuasive, particularly noting that the arguments of counsel cannot take the place of evidence in the record. Applicants provide herewith a declaration of inventor Dr. Henry E. Young stating and evidencing that the pluripotent PPELSCs have not been demonstrated to form gametes. In fact, as established in the Declaration, attempts by the inventor to identify the formation of gametes from the pluripotent embryonic-line stem cells of this invention, at the time of filing and subsequent to the date of

filing, have been unsuccessful. The inventor has, however, independently identified a distinct population of stem cells, BLSCs, capable of giving rise to all somatic lineages as well as functional gametes, and established that the assays applied to PPELSCs to evaluate formation of gametes, which generate negative results when screening PPELSCs, give positive results with the BLSCs. Applicants PPELSCs do not give rise to functional gametes, as stated and recited in the claims.

In view of the foregoing remarks, Applicants submit that the Examiner's 112, first paragraph, rejections are obviated and should be withdrawn.

The §102 Rejections

The Examiner has maintained his rejection of claims 14-16 under 35 U.S.C. 102(b) as being anticipated by Capecchi et al [Scientific American 270(3): 34-41 (1994)]. Capecchi teaches the inactivation of target genes by homologous recombination and the insertion of a *neo* resistance gene, which serves as a positive selection marker, in mouse ES cells. The Examiner asserts that the claimed cells are not distinguished from those taught by Capecchi. Applicants respectfully disagree and again assert that Capecchi et al does not anticipate claims 14-16. Applicants again argue that totipotent cells, including ES cells, can and do give rise to gametes by definition, where the pluripotent embryonic-like stem cells of Applicants cannot. The Examiner asserts that Applicants claims require only a single cell that does not give rise to functional gametes. Applicants respectfully disagree, however, for clarification have amended claims 14-16 to refer to cells. Also, Applicants underscore that the claimed ELSCs when grown under inducing conditions as a population of isolated cells do not form gametes, as further evidenced by the inventor's declaration submitted herewith. ES cells are totipotent and can form gametes, while pluripotent embryonic-like stem cells of this invention are pluripotent, not totipotent, and cannot form gametes. This is a distinction and difference in fact. Applicants PPELSCs are not taught or anticipated by the ES cells of the Capecchi et al reference, totipotent ES cells do not anticipate a pluripotent cell – they are distinct in character and differentiative capacity.

Claims 14-16 are again rejected under 35 U.S.C. 102(b) as being anticipated by Piedrahita et al [Biol of Reprod 58:1321-1329 (1998)], which teaches the generation of

transgenic porcine chimeras using primordial germ cell (PGC)-derived colonies. The Examiner asserts that Piedrahita et al anticipates the claimed invention because Piedrahita's cells are considered pluripotent and states "furthermore, although pluripotent cells have the ability to colonize the germline (as stated by Piedrahita, and cited by Applicants), the cells also have the ability to differentiate to other cells, as evidenced by the production of chimeric animals". Applicants respectfully submit that the Piedrahita et al cells are absolutely distinct from the pluripotent embryonic-like stem cells of the instant Application. Piedrahita teaches that the chimeric cells contributed to the germ line. Thus, PGCs of Piedrahita, similar to ES cells, are totipotent, forming cells from all three germ layers – ectoderm, endoderm, and mesoderm – and forming gametes to contribute to the germ line. The pluripotent embryonic-like stem cells of the instant Application differentiate to cells derived from all of the endodermal, ectodermal and mesodermal lineages, but cannot form gametes and thus do not and cannot contribute to the germ line. The PPELSCs do not possess all the capabilities of the Piedrahita PGCs. The cells of the Piedrahita et al reference are distinct from and do not teach or anticipate the PPELSC stem cells identified and claimed by Applicants.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's 102 rejections are obviated and should be withdrawn.

The §103 Rejections

The Examiner has maintained his rejection of claims 14-17 as unpatentable under 35 U.S.C. 103(a) over Shamblott [PNAS 95:13726-13731 (1998)] in view of Sambrook et al [Molecular Cloning, Book 3, 1989]. The Examiner remarks and asserts that the primordial germ cells (PGCs) of Shamblott are not considered totipotent, but are pluripotent, because they do not produce extra embryonic membranes, tissues, the embryo proper and all postembryonic tissues and organs. In fact, what is relevant for the claims as set out is whether the cells of Shamblott can form gametes – the pluripotent embryonic-like stem cells of Applicants cannot form gametes. Sambrook teach methods of transfecting mammalian cells with any gene of interest. The Examiner remarks that the instant claims do not provide any requisite characteristics of the claimed stem cells such that they would be distinguished from the cells taught by Shamblott. Applicants respectfully disagree and assert that the cells identified and claimed by Applicants are

distinguished from the Shamblott PGC cells and are not rendered obvious by the combination of the Shamblott and Sambrook references. The pluripotent embryonic stem cells are distinct from embryonic stem cells and primordial germ cells, particularly in that they are pluripotent and are not totipotent – they do not give rise to functional gametes. Also, the Examiner states that the claims of Applicants only require a single cell that does not give rise to functional gametes and this limitation is fulfilled by the combined teachings of Shamblott and Sambrook et al. Applicants respectfully disagree, however, for clarification have amended claims 14-16 to refer to cells, which serves to clarify that Applicants refer to a population of cells. Also, Applicants underscore that the claimed ELSCs when grown under inducing conditions as a population of isolated cells do not form gametes, as further evidenced by the inventor's declaration submitted herewith.

The Examiner again rejects claims 14-17 under 35 U.S.C. 103(a) as being unpatentable over Thomson [Reference BR on Applicants' IDS filed 7/3/03, PNAS USA 92:7844-7848 (1995)] taken with Sambrook [Molecular Cloning, Book 3, 1989]. The Examiner remarks on page 15 of this Office Action that the "cells of Thomson are not considered totipotent, but are pluripotent, because they do not produce extra embryonic membranes, tissues, the embryo proper and all postembryonic tissues and organs". Again, the Examiner states that "furthermore, although pluripotent cells have the ability/capability to colonize the germline, pluripotent cells also have the ability to differentiate to other cells, as evidenced by the production of chimeric animals". Applicants submit that the Examiner is factually incorrect. Pluripotent cells do not have the ability/capability to colonize the germline. Totipotent cells have the ability/capability to colonize the germline. What is relevant for the claims as set out, in fact and as to 35 U.S.C. 102 and 103, is whether the cells of Thomson can form gametes – the claimed pluripotent embryonic-like stem cells of Applicants cannot form gametes. Applicants again assert that the claimed pluripotent embryonic-like stem cells are distinct and unobvious from the cells of Thomson, which are ES cells and can colonize the germline. Furthermore, PPELSCs are not made obvious by the combination of ES cells taught in Thomson with the transfection of mammalian cells taught by Sambrook. ES cells are totipotent and are capable of giving rise to all somatic lineages (ectodermal, endodermal and mesodermal) as well as functional gametes. The pluripotent embryonic-like stem cells of the present invention are pluripotent and are capable of

differentiation to somatic cells of any endodermal, ectodermal, mesodermal lineage, but do not give rise to functional gametes. The combination of Thomson and Sambrook does not make obvious the genetically engineered pluripotent embryonic-like stem cells as claimed by Applicants.

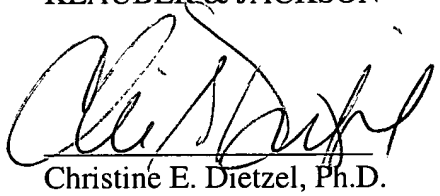
In view of the foregoing amendments and remarks, Applicants submit that the Examiner's 103 rejections are obviated and should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Should the Examiner feel that further issues remain upon a review of this Response, he is invited to call the undersigned at the number listed below to effect their resolution. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,

KLAUBER & JACKSON



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